Burden of antituberculosis and antiretroviral drug-induced liver injury at a secondary hospital in South Africa

Charlotte Schutz
MBChB; DipHIVMan(SA)
Student Number: schcha019

Mini-dissertation presented for the degree of

Masters Degree in Public Health (Clinical Research)

in the School of Public Health and Family Medicine

August 2012

Supervisor:
Graeme Meintjes

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UNIVERSITY OF CAPE TOWN

Department of Medicine
Division of Infectious Diseases & HIV Medicine

Graeme Meintjes MBChB MRCP(UK) FCP(SA) DipHIVMan(SA)
Clinical Research Fellow and Honorary Senior Lecturer
Institute of Infectious Diseases and Molecular Medicine
Faculty of Health Sciences
Observatory 7925 • Cape Town • South Africa
Telephone: +27 21 406 6079
Facsimile: +27 21 692 0289
Email: graemein@mweb.co.za

December 2009

Professor Blockman
UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Research Ethics Committee
E52- 23 Old Main Building
Groote Schuur Hospital
Observatory, 7925

Dear Professor Blockman

We wish to request permission from the Research Ethics Committee to perform a retrospective observational study of all patients who presented with hepatitis at GF Jooste hospital during 2009. This study will aim to describe the numbers of patients seen with hepatitis, the spectrum of causes of hepatitis, outcome, and the current burden on the health care system.

We will review case notes and laboratory records of all patients who were seen at GF Jooste during 2009 with an ALT of more than 200 and or total billirubin of more than 50.
We will ascribe the most likely cause for hepatitis in each case, look at the relation of hepatitis to TB medication and ART, the duration of hospital stay and outcome.

The focus will be to find out how many HIV and TB co infected patients present with drug induced hepatitis due to TB medication and ART. Our current clinical impression is that this is a frequent treatment complication in our setting and is associated with long hospital stays and lengthy drug rechallenges. However, this has not been formally described in our setting. With this study we will build a data base from which we can plan a future prospective study to look more in depth at causes of drug induced hepatitis, management thereof and the role of liver biopsy in this setting.

This study is strictly a retrospective data analysis and will be conducted according to GCP/ICH guidelines.

Yours sincerely

Signed by candidate

Signature removed

Graeme Meintjes
MBChB MRCP(UK) FCP(SA) DipHIVMan(SA)
Infectious Diseases Physician
(Supervisor)

Dr Charlotte Schutz
MBChB, DipHIVman(SA)
Infectious Diseases Principal Medical Officer GF Jooste Hospital
(Lead Investigator)

Other co-investigators:
Professor Robert Wilkinson
Dr Chris Kenyon
Dr Suzaan Marais
Dr Zahira Ismail

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: nosi.tywabi@uct.ac.za

18 December 2009

REC REF: 522/2009

Dr G Meintjes
Dept of Medicine
Division of Infectious Diseases & HIV Medicine

Dear Dr Meintjes

PROTOCOL TITLE: A RETROSPECTIVE OBSERVATIONAL STUDY OF ALL PATIENTS WHO PRESENTED WITH HEPATITIS AT GF JOOSTE HOSPITAL DURING 2009.

Thank you for submitting your study to the Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above mentioned study.

Approval is granted for one year until 24 December 2010.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

pp

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

FHS017: Annual Progress Report

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
☐ Approved	Annual progress report		
☐ Not approved	See attached comments		
Expiry date			
Chairperson of the HREC signature		Date	

Principal Investigator to complete the following:

1. Protocol information

Date	17 July 2012
HREC REF Number	522/2009
Protocol title	Burden of Tuberculosis and Antiretroviral Drug-Induced Liver Injury at a Secondary Hospital in South Africa
Protocol number (if applicable)	
Principal Investigator	Charlotte Schutz (Supervisor: Graeme Meintjes)
Department / Office Internal Mail Address	CIDRI Office, IIDMM, UCT Medical School

1.1 Does this protocol receive US Federal funding?	☐ Yes	√ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
√	Data collection is complete, data analysis only

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		318 records reviewed
Total number of records or specimens collected, reviewed or stored since last progress report		318 records reviewed
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	√ Yes	☐ No

4. Signature

Signature of PI	CSchutz	Date	17/07/2012
Signature of Supervisor (if PI is a student)		Date	

UNIVERSITY OF CAPE TOWN
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FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report
Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637, IRB0000 1938)			
☑ Approved	Annual progress report		
☐ Not approved	See attached comments		
Expiry date	15 JULY 2013		
Chairperson of the HREC signature		Date	18/7/2012

Principal Investigator to complete the following:

RESEARCH ETHICS COMMITTEE
2012 -07- 18
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

1. Protocol information

Date	17 July 2012
HREC REF Number	522/2009
Protocol title	Burden of Tuberculosis and Antiretroviral Drug-Induced Liver Injury at a Secondary Hospital in South Africa
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Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	√ Yes	☐ No

4. Signature

Signature of PI	CSchutz	Date	17/07/2012
Signature of Supervisor (if PI is a student)		Date	

PART A: Protocol

Burden of antituberculosis and antiretroviral drug-induced liver injury at a secondary hospital in South Africa

Aims:

1. To determine the proportion of patients who present with TB treatment and or ART-associated drug-induced liver injury (DILI) amongst all patients presenting with significant liver injury to GF Jooste Hospital during the study period.
2. To describe baseline clinical characteristics and management of TB treatment and or ART-associated DILI patients.
3. To describe the in-patient and 3-month mortality of TB treatment and or ART-associated DILI patients.

Background and Rationale:

GF Jooste Hospital is a public sector referral hospital and serves a densely populated area with a high burden of HIV and tuberculosis (TB). ART rollout in the Western Cape started in 2001/2002 at two pilot clinics and is now well established (1). Many patients are on concomitant TB treatment and ART. At ART clinics in the referral area 25-40% of patients are on TB treatment when they start ART (2, 3).
At GF Jooste hospital many HIV positive patients are seen who are on TB treatment and or ART, and present with symptomatic liver dysfunction. Patients are on multiple hepatotoxic drugs, may have multiple opportunistic infections, systemic sepsis and hepatic TB immune reconstitution disease also plays a role. Anecdotally, these patients are complex to manage, require frequent specialist input, spend a long time in hospital and have high mortality. Management guidelines are based on expert opinion and is not evidence based. In practice management relies heavily on the attending clinicians' experience and clinical judgment and management often differ widely between clinicians.
Mortality could be due to progression of TB and or HIV because of interruption of effective therapy, other opportunistic infections or hospital acquired infections. Few early liver biopsies are done and it is not known if early liver biopsies would aid by guiding management of these patients. Prospective studies are urgently needed to guide management in these patients.
The burden of TB treatment and or ART-associated drug induced liver injury in this setting has not been described to our knowledge, neither has management, outcome or mortality. This study was performed to aid planning of prospective studies in this field.

Study Site:

GF Jooste Hospital is a public sector referral hospital, which serves a largely socio-economically disadvantaged population of 1.2 million people. In Khayelitsha, which is the largest of the areas referring to GF Jooste Hospital, the TB notification rate is 1 600/100 000 and the antenatal HIV seroprevalence is

33% (4). Patients from surrounding ART and TB clinics who present with symptomatic liver dysfunction are referred to GF Jooste Hospital where liver function tests are performed. Based on the results of the liver function tests and clinical condition, patients are either admitted, or managed as outpatients. GF Jooste Hospital has an Infectious Diseases Referral Unit at which some patients with liver dysfunction could be managed as outpatients.

Design:

Retrospective observational study.

Methods:

Results of all liver function tests (LFT) performed at the GF Jooste Hospital National Health Laboratory Service laboratory from 1 January to 30 June 2009 were reviewed. Records for all patients who met criteria for significant liver dysfunction (see case definition below) were reviewed and data was extracted with a data extraction sheet developed for the study (see appendix A & B).

The following information was added to the protocol after protocol approval in response to a request from an external reviewer:
The liver function tests were retrieved with a search function from the NHLS database. This produced a list of all liver function tests performed at GF Jooste hospital for a specific time period. The researcher sorted through this list manually to identify all values that met study criteria and to eliminate duplicates. Permission was obtained from the local NHLS laboratory manager.

Inclusion Criteria:

1. Presence of significant liver dysfunction on GF Jooste laboratory records (refer to case definition below).
2. Patient seen and managed at GF Jooste Hospital from 1 January 2009 – 30 June 2009.

Case definitions:

Significant liver dysfunction
Liver dysfunction was defined as significant hepatocellular or cholestatic liver injury. Significant was defined as resulting in Grade 3 or 4 elevation of alanine amino transferase (ALT) and or total billirubin (TBR). The values are ALT≥200 U/l (>5 times the upper limit of normal and indicative of hepatocellular injury), and TBR≥44 µmol/l (>2.5 times the upper limit of normal and indicative of cholestatic injury) (5). The Division of AIDS table for grading he severity of Adult and Pediatric Adverse Events was used to determine these cut-off points, see appendix C & D. Patients who fulfilled one or both criteria were included. The rationale for the case definition was that drug-induced liver injury may present with either hepatocellular or cholestatic liver function test results and at GF Jooste Hospital it is clinical practice to generally not request full liver function

tests on patients to save laboratory costs. In practice an ALT is done to screen for hepatocellular injury and total billirubin to screen for cholestatic injury.

TB treatment or ART-associated liver dysfunction
Patient was managed as TB treatment and or ART-associated drug induced liver injury (DILI) by the admitting team, evident by changing or stopping TB treatment and or ART during the hospital stay.

Other causes of liver dysfunction
A cause other than TB treatment and or ART-associated DILI is identified as the primary cause of liver injury and the admitting team's treatment and management is aimed at this cause. Thus, patients receiving TB treatment and or ART who are admitted with another probable cause of liver injury and whose TB treatment and or ART is continued unaltered, are included in this category.

Sepsis
Sepsis was documented when the clinical presentation was compatible with sepsis and the admitting team managed infection as the primary cause of illness.

Hepatic Encephalopathy
The admitting team documented hepatic encephalopathy or signs and symptoms compatible with encephalopathy.

Determination of Outcome:

Clinical management and outcome data were ascertained by review of patient records. In-hospital and 3-month (within 90 days of presentation) mortality were recorded for TB treatment and or ART-associated DILI patients, including the cause of death where possible. Only in-hospital mortality was recorded for patients with liver injury due to other causes. Three-month retention in care was also recorded for the TB treatment and or ART associated DILI group. In the case of TB treatment and or ART-associated DILI, the Clinicom and eKapa electronic databases were consulted to ascertain follow-up and mortality documented elsewhere in the Western Cape. Loss to follow-up was defined as inability to trace any patient data after discharge but within 3 months of presentation.

Statistical Analysis:

Frequency statistics and survival analysis will be performed with STATA 11.1 software (2009).

Appendices: (Following the protocol):

- Data capture sheet for: GFJ Hepatitis Study: Initial Episode of Hepatitis/Cholestasis
- Data capture sheet for: GFJ Hepatitis Study: Subsequent Episode of Hepatitis/Cholestasis

- Division of AIDS Table for Grading the severity of Adult and Pediatric Adverse Events. Publish Date: December, 2004
- Laboratory Normal Value Ranges used at GF Jooste Hospital.

References

1. Bekker LG, Orrell C, Reader L, Matoti K, Cohen K, Martell R, et al. Antiretroviral therapy in a community clinic--early lessons from a pilot project. S Afr Med J. 2003 Jun;93(6):458-62.
2. Lawn SD, Bekker LG, Middelkoop K, Myer L, Wood R. Impact of HIV infection on the epidemiology of tuberculosis in a peri-urban community in South Africa: the need for age-specific interventions. Clin Infect Dis. [Research Support, N.I.H., Extramural
Research Support, Non-U.S. Gov't]. 2006 Apr 1;42(7):1040-7.
3. Boulle A, Van Cutsem G, Hilderbrand K, Cragg C, Abrahams M, Mathee S, et al. Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa. Aids. 2010 Feb 20;24(4):563-72.
4. Department of Health, 2009. 2008 National Antenatal Sentinel HIV and Syphilis
Prevalence Survey, South Africa.
5. AIDS Do. DAIDS Table for Grading Adult and Pediatric Adverse Events. Version 1.0. 2004 [cited 2011 28 December 2011]; Available from: http://rsc.tech-res.com/Document/safetyandpharmacovigilance/Table_for_Grading_Severity_of_Adult_Pediatric_Adverse_Events.pdf.

TB or ART DILI	
Other	

Complete	
Incomplete	
GSH/Carnation/KDH folder needed	
Busy with 3 month f/up	

GFJ Hepatitis Study Initial Episode

1. Name_____
   GFJ Folder number_____
   DOB_____
   Patient Sticker

   - Date of presentation with hepatitis _____
   - Was patient admitted? Yes/No
   - Date of discharge/death/transfer/abscondment _____

2. HIV status at presentation? Positive/Negative/Not tested
   - Most recent CD4 count _____Date of CD4 _____

3. On ART at presentation? Yes/No/Unknown
   - Date started _____

   Regimen at presentation:

AZT/3TC	
AZT/DDI	
D4T/3TC	
TDF/3TC	
NVP	
EFV	
Lop/Rit	
Other	
Unknown	

   If other, name medication _____
   _____

4. On TB treatment at presentation? Yes/No/Unknown
   - Date started _____

   Regimen at presentation:

Rif/INH/EMB/PZA	
Rif/INH/EMB/PZA + STREP	
Rif/INH	
Rif/INH/EMB	
MDR	
Other	
Unknown	

   If other TB medication, name medication _____

5. Cotrimoxazole Yes/No/Unknown
   - Primary prophylaxis? Yes/No
   - Secondary prophylaxis? Yes/No
   - Treatment? Yes/No

6. List all additional medication on presentation _____
   _____
   _____

7. Documented herbal medication/traditional medicine/OTC medication? Yes/No/Unknown
   List_____
   _____

8. If TB treatment or ART NOT the cause of hepatitis, what is the most likely primary cause of hepatitis?

Cotrimoxazole	
Paracetomol	
Alcohol	
TB IRIS	
Viral hepatitis (A,B,C)	
Sepsis	
Toxins	
Disseminated tuberculosis	
Other medication	
Other cause	
Unknown	

Name other cause _____
Name other medication _____
Details _____
_____
_____

Possible contributing factors to hepatitis (differential diagnosis)

- _____
- _____
- _____

Outcome

Died during initial admission	
Discharged	
Referred to another hospital	
Absconded	

Date of last record of patient _____
Cause of death _____

IF QUESTION 8 ANSWERED, STOP QUESTIONAIRE HERE

9. LFT values:

	Presentation	Peak (this episode)
AST		
ALT		
GGT		

ALP		
TBR		
INR		

- Hepatic encephalopathy at presentation? Yes/No

- If INR >1.4, is there any reason for abnormal INR apart from liver dysfunction? (eg CCF/Warfarin/DIC) Yes/No
  Reason_____

10. Hepatitis studies
    - Hep B sAg
    - Hep B eAg
    - Hep C Ab

Pos	Neg	N/D
Pos	Neg	N/D
Pos	Neg	N/D

11. Outcome

Died acutely (during initial admission)	
Died during follow up (3m)	
Discharged and known to be alive and in care (3 m)	
Discharged, seen as outpatient, LTFU (3 m)	
Discharged with no information after discharge	
Absconded	

- Cause of death _____
- Date of last record of patient _____

12. Management

TB treatment:

- Was treatment stopped completely? Yes/No
- Date stopped _____
- Changed to liver safer medication? Yes/No
- Date started _____
- Name liver safer medication _____
  _____

Taking at presentation?			Stopped?		Rechallenged or started?		Tolerated?	
Rif	Yes	No	Yes	No	Yes	No	Yes	No
INH	Yes	No	Yes	No	Yes	No	Yes	No
EMB	Yes	No	Yes	No	Yes	No	Yes	No
PZA	Yes	No	Yes	No	Yes	No	Yes	No
Strep	Yes	No	Yes	No	Yes	No	Yes	No
MDR	Yes	No	Yes	No	Yes	No	Yes	No
Bactrim	Yes	No	Yes	No	Yes	No	Yes	No

TB drug rechallenge not done? Yes/No
Reason _____

ART:

Unchanged?	
Completely stopped?	
NVP changed to EFV?	
NVP interrupted and EFV restarted later?	
EFV changed to Lop/Rit?	
EFV interrupted and restarted on EFV later?	
EFV interrupted and started on Lop/Rit later?	
Other	

Details of other _____
_____

13. Time taken to get back onto optimal therapy
    - TB treatment (Rif based) Date _____
    - ART (Tripple therapy/PI based) Date _____
    - If NOT back on optimal therapy, list regimen and reason

      TB treatment_____
      _____

      ART_____
      _____

    - Loss to follow up during rechallenge? Yes/No

14. Additional relevant investigations Yes/No

Liverbiopsy	Conclusion	
ERCP	Conclusion	
USS abdomen	Conclusion	
CT abdomen	Conclusion	

15. Outpatient follow up related to hepatitis (within 3 months after initial presentation) Yes/No
    Number of visits _____

16. Possible contributing factors to hepatitis? (differential diagnosis eg TB IRIS, heavy ETOH, chronic Hep B etc)
    - _____
    - _____
    - _____
    - _____

17. Did patient have a subsequent episode of abnormal LFT's investigated at hospital? Yes/ No
    If yes, complete subsequent episodes form

TB or ART DILI	
Other	

Complete	
Incomplete	
GSH/Carnation/KDH folder needed	
Busy with 3 month f/up	

GF Jooste Hepatitis Study

Subsequent Episodes of hepatitis

1. Name_____
   GFJ Folder number_____
   DOB_____
   Patient Sticker

   Date of presentation with hepatitis _____

   Was patient admitted? Yes/No

   Date of discharge/death _____

2. Likely primary cause of hepatitis
   - _____

   Contributing factors/differential diagnosis
   - _____
   - _____

3. Drug interruptions/changes?
   - TB Treatment Yes/No

   Details _____
   _____

   - ART Yes/No

   Details _____
   _____

   - Other Yes/No

   Details _____
   _____

4. Additional investigations done? Yes/No

Investigation	Conclusion
USS abdomen	
CT abdomen	
Liver biopsy	
ERCP	
Other	

5. Followed up as outpatient?Yes/No
   Number of visits (3 months after this episode) _____

6. Outcome

Died during initial admission	
Discharged	
Referred to another hospital	
Absconded	

   - Date of last record of patient _____
   - Cause of death_____

7. Other relevant information?
   _____
   _____
   _____

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

Quick Reference

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE grading table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

General Instructions

Estimating Severity Grade

If the need arises to grade a clinical AE that is not identified in the DAIDS AE grading table, use the category "Estimating Severity Grade" located at the top of Page 3. For AEs that are not listed in the table but will be collected systematically for a study/trial, protocol teams are highly encouraged to define study-specific severity scales within the protocol or an appendix to the protocol. (Please see "Template Wording for the Expedited Adverse Event Reporting Section of DAIDS-sponsored Protocols".) This is particularly important for laboratory values because the "Estimating Severity Grade" category only applies to clinical symptoms.

Grading Adult and Pediatric AEs

The DAIDS AE grading table includes parameters for grading both Adult and Pediatric AEs. When a single set of parameters is not appropriate for grading specific types of AEs for both Adult and Pediatric populations, separate sets of parameters for Adult and/or Pediatric populations (with specified respective age ranges) are given in the table. If there is no distinction in the table between Adult and Pediatric values for a type of AE, then the single set of parameters listed is to be used for grading the severity of both Adult and Pediatric events of that type.

Determining Severity Grade

If the severity of an AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

Definitions

Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding. Young Children Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
LLN	Lower limit of normal
Medical Intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE.
NA	Not Applicable
Operative Intervention	Surgical OR other invasive mechanical procedures.
ULN	Upper limit of normal
Usual Social & Functional Activities	Adult Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc. Young Children Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

Contents

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

CLINICAL

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE grading table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6 C	38.7 – 39.3 C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

CLINICAL

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm^2 – 81cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children > 10 cc/kg) indicated
Hypertension				
Adult > 17 years (with repeat testing at same visit)	> 140 – 159 mmHg systolic OR > 90 – 99 mmHg diastolic	> 160 – 179 mmHg systolic OR > 100 – 109 mmHg diastolic	> 180 mmHg systolic OR > 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Pediatric ≤ 17 years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval				
Adult > 16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block

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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Prolonged QTc				
Adult > 16 years	Asymptomatic, QTc interval 0.45 – 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 years	Asymptomatic, QTc interval 0.450 – 0.464 sec	Asymptomatic, QTc interval 0.465 – 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences

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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea				
Adult and Pediatric ≥ 1 year	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Pediatric < 1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

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Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – **Pediatric ≤ 16 years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

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Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset) – **Adult ≥ 18 years** See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 – 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (known pre-existing seizure disorder) – **Adult ≥ 18 years** For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure – **Pediatric < 18 years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Usual Social & Functional Activities – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70 – 80%	FEV1 or peak flow 50 – 69%	FEV1 or peak flow 25 – 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress				
Adult ≥ 14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss				
Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences

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Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

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Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).

Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption < 25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA

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CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY	***Standard International Units are listed in italics***			
Absolute CD4+ count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm^3 *< 0.350 x 10^9/L*
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Infant[*†], 2 – ≤ 7 days	1,250 – 1,500/mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/mm^3 *< 0.750 x 10^9/L*
Infant[*†], 1 day	4,000 – 5,000/mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9 – 3.999 x10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/mm^3 *< 1.500 x 10^9/L*
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin (Hgb)				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *1.32 – 1.55 mmol/L*	7.5 – 8.4 g/dL *1.16 – 1.31 mmol/L*	6.50 – 7.4 g/dL *1.01 – 1.15 mmol/L*	< 6.5 g/dL *< 1.01 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *1.55 – 1.69 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *0.39 – 0.53 mmol/L*	9.0 – 9.9 g/dL *1.40 – 1.54 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *0.54 – 0.68 mmol/L*	7.0 – 8.9 g/dL *1.09 – 1.39 mmol/L* OR Any decrease ≥ 4.5 g/dL *≥ 0.69 mmol/L*	< 7.0 g/dL *< 1.09 mmol/L*
Infant[*†], 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *1.32 – 1.46 mmol/L*	7.0 – 8.4 g/dL *1.09 – 1.31 mmol/L*	6.0 – 6.9 g/dL *0.93 – 1.08 mmol/L*	< 6.00 g/dL *< 0.93 mmol/L*

[*] Values are for term infants.

[†] Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *1.47 – 1.63 mmol/L*	8.0 – 9.4 g/dL *1.24 – 1.46 mmol/L*	7.0 – 7.9 g/dL *1.09 – 1.23 mmol/L*	< 7.00 g/dL *< 1.09 mmol/L*
Infant*†, 1 – 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *1.86 – 2.02 mmol/L*	10.0 – 11.9 g/dL *1.55 – 1.85 mmol/L*	9.0 – 9.9 g/dL *1.40 – 1.54 mmol/L*	< 9.0 g/dL *< 1.40 mmol/L*
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*
CHEMISTRIES	***Standard International Units are listed in italics***			
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Bilirubin (Total)				
Adult and Pediatric > 14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN

*Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

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LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Infant*†, ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
Infant*†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high (corrected for albumin)				
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Infant*†, < 7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low (corrected for albumin)				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL *< 1.53 mmol/L*
Infant*†, < 7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥ 18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Pediatric < 18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Creatine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*

*Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Glucose, serum, low				
Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Infant*†, < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Lactate	< 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
LDL cholesterol (fasting)				
Adult ≥ 18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Pediatric > 2 - < 18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low	1.2 – 1.4 mEq/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 mEq/L *< 0.30 mmol/L*
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low				
Adult and Pediatric > 14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL *< 0.32 mmol/L*
Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Pediatric < 1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Potassium, serum, high	5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low	3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high	146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*
Sodium, serum, low	130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L *≤ 120 mmol/L*
Triglycerides (fasting)	NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL *> 13.56 mmol/L*
Uric acid	7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL *> 0.89 mmol/L*

*Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS PUBLISH DATE: DECEMBER, 2004

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
URINALYSIS	***Standard International Units are listed in italics***			
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection				
Adult and Pediatric ≥ 10 years	200 – 999 mg/24 h *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h *> 3.500 g/d*
Pediatric > 3 mo - < 10 years	201 – 499 mg/m^2/24 h *0.201 – 0.499 g/d*	500 – 799 mg/m^2/24 h *0.500 – 0.799 g/d*	800 – 1,000 mg/m^2/24 h *0.800 – 1.000 g/d*	> 1,000 mg/ m^2/24 h *> 1.000 g/d*

*Values are for term infants.

† Use age and sex appropriate values (e.g., bilirubin), including preterm infants.

Jooste Hospital: Results

Patient name:

Year :

Folder no:

month											
day											
Haematology											
Hb											
MCV 82-100fL											
WBC 4-11x10^9/L											
Platelets 140-400x10^9/L											
INR											
PTT											
Chemistry											
Na 135-145mmol/L											
K 3.5-5.5mmol/L											
Urea 2-5mmol/L											
Creatinine 50-130µmol/L											
CRP 0-10mg/L											
Glucose 3.5-6.0mmol/L											
Serum ketones											
Liver											
AST 0-40U/L											
ALT 0-40U/L											
GGT 10-35U/L											
Alk phosphatase 40-120U/L											
Bilirubin total 3-17µmol/L											
Bilirubin conj 0-6µmol/L											
Total protein 60-80g/L											
Albumin 35-55g/L											
CSF											
Polymorphs 0											
Lymphocytes $<5/mm^3$											
RBCs 0											
Protein 0.15-0.45g/L											
Glucose 2.2-3.9g/L											
India Ink											
CLAT											
VDRL/RPR											
Other											

Part B: Structured literature review

Objectives

The objective of this literature review is to summarize key concepts related to tuberculosis (TB) treatment and or antiretroviral therapy (ART)-associated drug-induced liver injury (DILI) from currently published literature with the focus on HIV as a risk factor for TB DILI and concomitant ART and TB treatment as a risk factor for DILI. This review serves as an introduction to the research study that follows. The study was conducted at GF Jooste Hospital and assessed the burden of TB treatment and or ART-associated DILI at a referral hospital in South Africa.

Search Methods & Selection Criteria:

A Pubmed search was performed with key words and combinations of HIV, tuberculosis, hepatotoxicity and drug induced liver injury. All studies that reported hepatotoxicity and included 1) adult HIV positive patients on antiretroviral therapy and or; 2) adult patients on TB treatment and or; 3) adult patients on concomitant TB treatment and antiretroviral therapy, were reviewed. Studies including paediatric patients, studies concerning TB preventative therapy and studies in TB patients which did not include any HIV-infected patients were not assessed for this review. References of relevant studies were also examined and used to find additional articles for this review. The methods used in this review did not meet the criteria for a systematic review.

Background:

Burden of tuberculosis and HIV:

An estimated 34 million people are HIV-infected globally (1). There were an estimated 8.8 million incident TB cases worldwide in 2010, of which an estimated 1.3 million cases occurred in people who were HIV-infected (2). In South Africa TB case notifications reached almost 400 000 per annum in 2010, with 61% of incident TB cases being HIV co-infected (2). In the Western Cape province TB prevalence at ART initiation is very high. Two large public sector antiretroviral (ART) clinics in Cape Town reported concomitant TB treatment in 25% and 40% of patients respectively, at time of ART initiation (3, 4). Forty-two percent of HIV-positive incident TB cases in South Africa received both ART and TB treatment in 2009, compared with 18% in 2008 (5) .

The importance of drug induced liver injury (DILI):

Multi-drug treatment for active TB has several well-known side effects. One of the most common and serious is hepatotoxicity (6). All classes of ART are potentially hepatotoxic (7). These overlapping toxicity profiles in often overlapping, multi-drug treatment regimens, cause complex clinical scenarios in patients who present with liver injury. Commonly used prophylactic medication like cotrimoxazole, fluconazole and other conditions like tuberculosis-associated immune reconstitution inflammatory syndrome (TB IRIS) and systemic sepsis may also contribute to liver dysfunction (8-10).

Clinical presentation and diagnosis of DILI:

Clinical presentation of DILI is non-specific and initially indistinguishable from liver injury due to other causes, like viral hepatitis (11, 12). DILI should always be considered in patients with liver dysfunction (13), especially in patients with

HIV infection and/or tuberculosis. There is no diagnostic test to distinguish DILI from other causes of liver dysfunction. Careful history taking (with focus on timing of initiation of all treatment regimens, including herbal medication and timing of symptom onset in relation to medication), physical examination and focused clinical investigations should rule out other causes of liver injury before making the diagnosis of DILI (13, 14).

Mechanisms of DILI:

Mechanisms of DILI are complex and poorly understood. It is likely that each drug has a unique mechanism of causing toxicity, which determines clinical presentation. Several drug targets have been identified and the pattern of cell injury depends on which target is affected by a specific drug. Each target triggers a different mechanism and thus a different pattern of hepatocyte injury. Manifestations of DILI in individuals are further influenced by demographic factors, genetic susceptibility and environmental factors (11, 13, 15, 16). First-line treatment for active TB in South Africa, includes rifampicin, isoniazid, ethambutol and pyrazinamide (17). Rifampicin, isoniazid and pyrazinamide are known hepatotoxic drugs. Isoniazid is thought to cause DILI through its toxic metabolites, acetylhydrazine or hydrazine (18). It is not well understood how rifampicin and pyrazinamide cause DILI (12). Antiretroviral treatment in South Africa includes nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI). NNRTI drugs (efavirenz and nevirapine) most commonly cause an allergic hepatitis, which is associated with rash and systemic symptoms (19). NRTI drugs (stavudine, didanosine, zidovudine and tenofovir), may cause mitochondrial toxicity with prolonged exposure, which results in a fatty liver

(20). This usually results in moderate elevations of liver enzymes. Importantly it has also been shown that ART naïve HIV-infected patients have underlying mitochondrial damage on liver biopsy (21): this may predispose to NRTI damage. It is unknown how PI's cause DILI and occurrence of DILI varies with specific PI used (7). Depending on the mechanism of DILI, there may be mainly hepatocellular injury, cholestatic injury or a mixed pattern. This manifests as either a rise in transaminases (alanine transaminase [ALT] and aspartate aminotransferase [AST]) in the case of hepatocellular injury, a rise in cholestatic enzymes (gamma glutamyl-transpeptidase [GGT], alkaline phosphatase [ALP] and or/total bilirubin [TBR]) in the case of cholestatic injury or rise in both (mixed picture).

Management of DILI:

If liver injury is severe, treatment needs to be interrupted. Failure to interrupt the offending drug may result in death (22). Treatment interruption for TB and or HIV carries the risk of disease progression and death (6) and drug resistance. Once liver enzymes have normalized, relevant treatment needs to be re-introduced, usually in a step-wise manner. Details of management and drug re-challenge will not be discussed in this literature review.

Occurrence of TB treatment associated DILI (TB DILI) and HIV as a risk factor for TB DILI:

a) Observational studies that included HIV-infected and HIV-uninfected patients (but HIV testing was not routinely done) and reported tuberculosis treatment-associated drug-induced liver injury (TB DILI): (summarized in table 1)

Schaberg et al retrospectively reviewed a cohort of 519 hospitalized TB patients in Germany. 200 patients were tested for HIV and 9 were HIV positive. Patient records were reviewed for adverse events severe enough to interrupt TB treatment and 55 (11%) cases of hepatotoxicity meeting this criterion occurred. HIV infection was not found to be a risk factor for development of severe adverse events, but the number of HIV-infected patients in this cohort was small (23).

A study by Yee et al in Canada reported on all serious side effects of first line tuberculosis treatment, which resulted in the treatment being stopped or adjusted, and amongst these was hepatotoxicity. HIV infection had an adjusted hazard ratio (aHR) of 3.8 (95% confidence interval [CI] 1.05-13.4) for the development of serious adverse events on TB treatment. The hazard ratio of HIV infection for the development of DILI, specifically, was not reported (24).

A study in Malaysia by Marzuki et al, report a 9.7% prevalence of TB DILI in a retrospective cohort of 473 TB patients. They selected all 46 cases of TB DILI and then randomly selected 138 controls in a nested case control study. They reported HIV infection as a significant independent risk factor for developing TB DILI with an odds ratio of 3.54 (95% CI = 1.25-10.05). There were 9 (20%) HIV-infected persons amongst the DILI cases and 8 (6%) amongst the controls (25).

De Castro et al reported 30 cases of DILI in a prospective cohort of 154 TB patients in Brazil. 19 cases of DILI occurred amongst 60 HIV-infected persons and 11 amongst 94 HIV uninfected persons. In this study HIV infection was an independent risk factor for the development of TB DILI with a risk ratio of 2.72 (95% CI=1.39-5.28) (26).

In an Iranian study by Baghaei et al, a TB DILI incidence of 13% was reported in a prospective cohort study of 761 patients. The definition used for diagnosis of DILI was not clear. Few patients were tested for HIV infection. Amongst those who were tested, DILI occurred in 7/43 (16%) HIV positive patients and in 54/196 (28%) HIV negative patients. HIV was not reported as a risk factor for TB DILI in this study (27).

Tostmann et al enrolled 112 TB patients prospectively in Tanzania and found no cases of DILI. There was a low HIV co-infection rate with 11 patients HIV co-infected, and none were taking ART at the start of the study. 6 participants started efavirenz based ART during the course of the study. Patients were only followed during the two-month intensive phase of TB treatment (28).

In a prospective study reported by Lorent et al in Rwanda there were 24 (9.5%) episodes of DILI amongst 253 tuberculosis cases. Twenty-two (8.7%) of these episodes occurred amongst HIV-infected patients. Two thirds of the cohort (167) people were HIV-infected. A third of HIV-infected patients were on ART at time of initiation of TB treatment, a third started ART during intensive phase of TB treatment and virtually all patients were on cotrimoxazole prophylaxis. HIV infection was an independent predictor for serious adverse events during first line tuberculosis treatment; in this cohort 64 (23%) patients developed serious adverse events and 58 of these patients were HIV-infected. The adjusted hazard

ratio for HIV as a predictor of serious adverse events was 2.43 (95% CI = 1.35-8.67; p-value = 0.009) (29).

b) Studies that directly compared TB DILI in HIV-infected and HIV uninfected patients (HIV testing routinely done): (summarized in table 2)

Perriens et al enrolled 523 TB patients prospectively in Zaire. 335 patients were HIV co-infected and this was prior to availability of ART. They do not mention the definition of hepatitis, but state that no hepatitis was seen in the cohort, although increased levels of ALT, AST and billirubin was sometimes seen. These liver enzyme elevations were not significantly associated with HIV infection (30).

In a prospective cohort study conducted in Haiti in 1990, Chaisson et al enrolled 427 TB patients of which 177 were HIV-infected. They found similar rates of DILI in both groups: 12% in the HIV-infected TB patients and 9% (not statistically significant) in the uninfected group. This was prior to availability of ART (31).

A retrospective study by Breen et al in the United Kingdom compared the occurrence of grade 3 and 4 adverse events (AE) during TB therapy between 156 HIV-TB co-infected patients and 156 HIV negative TB patients treated at the same facilities. They found an increased number of grade 3 and 4 adverse events amongst TB-HIV co-infected patients, 40% vs. 26% (p=0.008). However, there were 20 cases of DILI in each group and no excess treatment interruptions in the HIV-infected group. Seventeen co-infected patients had treatment interrupted due to DILI vs. 20 in the HIV negative group. Twenty-nine HIV-infected patients were on ART at initiation of TB treatment and a further 82 started ART within a median of two months of starting TB treatment. Of note, when stratified by

ethnic group, the black African population showed a difference between the groups, with more grade 3 and 4 AE's and more TB treatment interruptions in those HIV-infected, 43% vs. 21%, and 13% vs. 6%, respectively. The numbers of DILI cases in the black African group was not reported (32).

A prospective study in Ethiopia by Yimer at al enrolled 197 consecutive TB patients. All patients were tested for HIV and 103 (52.3%) were HIV positive. 34 cases of DILI occurred and 26 were in HIV-infected persons. HIV was an independent risk factor for developing TB DILI in multivariate analysis with an adjusted odds ratio of 3.6 (95% CI=1.5-8.5; p=0.002). There was no mention of antiretroviral therapy in this paper despite 80% of patients having a CD4 cell count of less than 200 cells/mm^3 (33).

A Brazilian case-control study by Coca et al analysed a cohort of 30 HIV positive TB patients and compared the occurrence of DILI with a control group of 132 HIV negative TB patients. They assessed the presence of DILI by using three different definitions of hepatotoxicity. The definitions were: a) ALT > three times the lower limit of normal (LLN), b) ALT > three times the upper limit of normal (ULN) and c) ALT >3 times ULN plus total billirubin >2 ULN. The first definition is not clinically relevant. Hepatotoxicity, using definition b) occurred in 6 (20%) HIV-infected and 12 (9.1%) uninfected persons and using definition c) in 6 (20%) HIV-infected and 11 (8.3%) uninfected persons. There was no mention of antiretroviral therapy or CD4 counts in this paper. HIV was not a risk factor for developing hepatotoxicity in this study (34).

Identifying risk factors for DILI in HIV-TB co-infected patients:

Studies that included only HIV-TB co-infected patients: (summarized in table 3)

Dean et al retrospectively reviewed 188 HIV-TB co-infected patients treated at HIV clinics in London from 1996-1999. 15% of patients were on ART at start of TB treatment and 45% started ART during TB therapy at a median of 2 months. Details of therapy were only available for 99 patients and of these 11 experienced DILI. In multivariate analysis female gender (OR 2.03; 95% CI=1.09-3.77) and concomitant TB and HIV treatment (OR 1.88; 95%=1.03-3.42) were independently associated with the development of adverse events (35).

Tostmann et al reports on hepatotoxicity in a randomized controlled trial initially reported by Boeree et al (36). The trial investigated cotrimoxazole prophylaxis at different doses in newly diagnosed smear positive TB patients. All patients were HIV-infected, but none were taking ART. They report 3 cases of grade 3 DILI and none with grade 4 DILI. 25% of patients either died or were lost to follow up during the trial and those who were lost to follow up were more likely to have had a high ALT at inclusion. It is likely that the rate of DILI in this trial was underestimated and DILI could have been due to TB medication or cotrimoxazole prophylaxis (37).

Pukenyte et al performed a retrospective observational study in France to determine the incidence and risk factors for severe liver toxicity in HIV-TB co-infected patients. One hundred and forty four patients who were treated for TB at 6 different hospitals over a 12-year period were included. The majority of patients were not on ART. Of 25 patients who were on ART 3 developed DILI. Concomitant treatment with ART was not associated with increased risk of DILI.

In multivariate analysis, independent risk factors for liver toxicity were abnormal ALT at baseline with adjusted hazard ratio (aHR) = 3.86 (95% CI=1.15–12.88; p=0.028), increased baseline billirubin levels with aHR = 4.34 (95% CI=1.13–16.7; p=0.033), and the concomitant use of fluconazole with TB treatment, aHR = 4.90 (95% CI=1.52–15.86; p=0.008) (38).

Moses et al performed a retrospective observational study in Malawi, which included all new adult TB patients (n= 156) registered in a rural hospital from June – December 2007. Patients were HIV-infected; ART-naive and received nevirapine based ART during TB treatment. Malawi used a fixed dose combination of stavudine, lamivudine and nevirapine as first line ART. Two patients developed grade 2 hepatotoxicity and 1 developed grade 3 toxicity, which was an incidence rate for grade 2-4 hepatoxicity of 4.2 per 10 years of follow up, 95% CI=1.4-13.1 (39).

Mankhatitham et al analyzed the hepatotoxicity data of the N2R trial conducted by Manosuthi et al (40). The N2R trial was a randomized controlled trial in Thailand which enrolled 142 HIV-infected TB patients receiving rifampicin based TB treatment during 2006 & 2007. Patients were randomized to start either nevirapine or efavirenz based ART. These patients had a high rate of chronic viral hepatitis. Five percent had chronic hepatitis B and 25% had chronic hepatitis C infection at baseline. There were 9 episodes of grade 3 or 4 transaminitis or hyperbilirubinaemia. Chronic hepatitis C at baseline was the only independent predictor of hepatotoxicity in this study with an adjusted odds ratio = 3.03 (95% CI=1.26-7.29) (41).

Yimer et al studied a prospective cohort of Ethiopian patients enrolled from 2004-2007. All patients were started on rifampicin based TB treatment and then

started on efavirenz based ART within 8 weeks of starting TB treatment. Out of 373 patients 20 developed severely elevated (more than 5 times the ULN) transaminases (likely TB DILI) prior to starting ART and were excluded from the analysis. The reason for this was that the investigators wanted to assess risk factors for developing DILI on concomitant TB treatment and ART. There were 106 cases of DILI on concomitant TB treatment and ART, of which 65 were severe DILI with transaminases more than 5 times the ULN. They identified female sex, low BMI, high efavirenz levels, high pre-treatment ALT/AST, low hemoglobin (Hb) and low albumin to be associated with development of DILI. It is not clear whether this was on univariate or multivariate analysis. They also performed a case control study analysing genetic variants with respect to drug metabolising status and found slow acetylation status, CYP2B6*6/*6 and ABCB13435TT genotypes to be predictors of DILI in this population. It is not clear how the patients were selected from the cohort for this case control study (42).

Concomitant TB treatment as a risk factor for DILI in patients on ART: Comparing DILI in patients on ART alone vs. patients on ART and TB treatment: (summarized in table 4)

Hoffman et al retrospectively reviewed a cohort of 868 HIV-infected patients in South Africa in an occupational setting (mainly men), who accessed ART through a work place programme. Twenty five percent of patients were on concomitant TB treatment and 17% of a randomly selected sub-group were hepatitis B co-infected. They found concomitant TB treatment and chronic hepatitis B infection to be independent predictors of grade 3 or 4 DILI with an adjusted hazard ratio of 8.5 (95% CI=2.7–27; p=<0.001) and 3.0 (95% CI=1.3–7.0; p=0.016) respectively (43).

Shipton et al performed a retrospective observational study in Botswana, analysing all patients in HIV care at a hospital in Gaborone from 2001 to 2004. They included all patients who were initially TB treatment and ART naïve and then started TB treatment during the study period and received concomitant ART. The control group with similar distribution of HIV viral load values were patients who received only ART treatment. TB treatment was initiated at a median of 81 days prior to ART. There were more episodes of hepatotoxicity in the group with concomitant TB treatment and ART as opposed to the ART-only group; 9% vs. 3% with p=0.05. Of note, there was no difference in rate of hepatotoxicity between patients taking efavirenz or nevirapine-based ART in either group (44).

Chu et al analyzed data from three large primary care ART clinics in the Western Cape province of South Africa to determine the occurrence of early hepatotoxicity on ART amongst 1809 ART naïve patients initiating nevirapine

based ART. Early hepatotoxicity was defined as ALT grade 0-2 at baseline, which increased to grade 3 or 4 within 102 days of starting ART. Early hepatotoxicity occurred with an incidence rate of 3.6-7.6 per 100 person years at the 102-day time point, depending on how regularly LFT's were measured. Concurrent TB treatment was not a risk factor for development of DILI in this study. The number of patients on concurrent TB treatment is not mentioned in the study, but 4 of the 26 cases of DILI occurred in patients on TB treatment (45).

Kalyesubula et al enrolled 240 ART-naive patients prospectively in Uganda and monitored liver function after starting ART. Two hundred and thirty eight patients (99.2%) were receiving cotrimoxazole prophylaxis and 13 (5%) received concomitant TB treatment. Patients on concomitant ART and TB treatment were more likely to develop DILI with an odds ratio of 16.0 (95% CI; 2.4-104.2,P<0.01) (46).

Mugusi et al performed a prospective study in Tanzania and classified 473 ART-naive HIV-infected patients with CD4 count < 200 cells/μL into 2 clinical categories, HIV only (n=253) and HIV-TB co-infected (n=220). There were 37 episodes of DILI of which 22 (10% incidence) occurred in the HIV-TB co-infected group and 15 (5.9% incidence) in the HIV-only group. This suggests more DILI in HIV-TB co-infected patients although this difference was not statistically significant (p-value = 0.07). Predictors of DILI in this cohort were chronic hepatitis C infection, higher WHO stage at presentation, history of weight loss and CYP2B6*6 genotype (47).

Discussion:

The incidence of TB DILI in HIV-infected and uninfected patients is not frequently reported and varies (range 0-19.5%), depending on the definition for DILI. Studies reporting the occurrence of TB DILI, which includes both HIV-infected and HIV uninfected participants, report conflicting data regarding HIV as a risk factor for TB DILI. Some studies report HIV infection as an independent risk factor for TB DILI and thus higher rates of TB DILI in HIV positive patients (with estimates of roughly two-fold increase among HIV-infected), while other studies report similar rates of TB DILI in the HIV-infected and uninfected TB patients. No obvious reason was found for this discrepancy in the literature reviewed. Genetic factors and other differences between the populations studied could be responsible for this discrepancy.

In studies including only HIV-TB co-infected patients several risk factors have been identified to be independently associated with development of DILI across different studies: female sex, concomitant TB treatment and ART, elevation of baseline ALT and AST, fluconazole use, higher plasma efavirenz level, higher efv/8-hydroxyefavirenz ratio, lower baseline hemoglobin, lower serum albumin, NAT2 slow-acetylator genotype and ABCB1 3435TT genotype. However, only a few studies have reported pharmacogenetic profiling of patients who develop DILI.

Several studies which compared patients on ART alone to patients on ART and TB treatment, report conflicting data regarding the risk of concomitant TB treatment and ART for the development of DILI. All the studies assessed for this aspect of the literature review were from the African continent and again there was no obvious explanation found for the discrepancies reported. It may be due

to genetic and other differences between populations studied, or differences in the case definitions used for DILI.

Conclusion:

Drug induced liver injury is a poorly understood clinical entity and the cause of a substantial burden of disease. Mechanisms by which most drugs cause liver injury are unknown. Some risk factors for development of drug induced liver injury have been described. However, more studies are needed to better define mechanisms and risk factors for DILI. The role of HIV infection in development of TB DILI and the role of concomitant TB treatment and ART in the development of DILI need to be clarified.

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Table 1: Observational studies that included HIV-infected and HIV-uninfected patients (but HIV testing was not routinely done) and reported tuberculosis treatment-associated drug-induced liver injury (TB DILI):

Reference Country	n	DILI among HIV positive	DILI among HIV negative	DILI Total	ART	HIV a significant risk factor for DILI?
(23) Germany	519	NR/9	NR/191	55 (11%)	NR	No
(24) Canada	430	NR/18	NR/149	12 (2.8%)	NR	[1]No
[2](25) Malaysia	473	9/46 HIV-infected among DILI patients	8/138 HIV-infected among controls	46 (9.7%)	NR	Yes
(26) Brazil	154	19/60	11/94	30 (19.5%)	29 on ART[3]	Yes
(27) Iran	761	7/43	54/196	99 (13%)	NR	No
(28) Tanzania	112	0/11	0/90	0	6 started ART during study	No
(29) Rwanda	253	22/167	2/86	24 (9.5%)	65 on ART; 55 started ART during study	Yes[4]

Legend for table 1:
n=number of patients in study.
DILI: Drug induced liver injury
DILI Total: Drug induced liver injury cases in total.
NR= not reported.
[1]Not statistically significant with adjusted hazard ratio [aHR]=4.3 (95% confidence interval [CI] 0.5 – 38). HIV was shown to be a risk factor for development of grade 3 or 4 adverse events with aHR =3.8 (95% CI 1.05-13.4)
[2]All cases of DILI were selected from the cohort and then controls were randomly selected for a case control study. Nine out of 46 patients with DILI were HIV-infected and 8 out of 138 controls were HIV-infected.
[3]All remaining patients except one started ART during TB treatment.
[4]HIV infection was an independent risk factor for development of serious adverse events (not DILI specifically) with aHR = 2.43 (95% CI = 1.35-8.67; p-value = 0.009).

Table 2: Studies that directly compared tuberculosis treatment-associated drug-induced liver injury (TB DILI) in HIV-infected and HIV-uninfected patients (HIV testing routinely done):

Reference Country	n	DILI among HIV positive	DILI among HIV negative	DILI Total	ART	HIV a significant risk factor for DILI?
(30) Zaire	523	0/335	0/188	0	None	No
(31) Haiti	427	12% of 177	9% of 250	21% of 427	None	No
(32) United Kingdom	312	20/156	20/156	40	[1]111	No
(33) Ethiopia	197	26/103	8/94	34	NR	Yes
[2](34) Brazil	162	6/30	12/132	18	NR	No

Legend for table 2:
n=number of patients in study
DILI: Drug induced liver injury
DILI Total: Drug induced liver injury cases in total
NR: Not reported
[1]29 on ART at the start of the study and 82 patients started on ART during study at a median of 2 months after initiating TB treatment.
[2]Three different definitions for DILI were used in this paper. The number of cases for definition b) reported in table, see detail in text.

Table 3: Identifying risk factors for DILI in HIV-TB co-infected patients: Studies that included only HIV-TB co-infected patients:

Reference Country	n	ART	DILI Total	Factors associated with increased risk to develop DILI
(35) United Kingdom	188	15% on ART; 45% started ART during TB treatment	11 (5.9%)	[1]Female sex: OR=2.03; 95% CI 1.09-3.77) Concomitant TB treatment and ART: OR=1.88; 95% 1.03-3.42)
(37) Malawi	579	No ART	[2]8 (1.4%)	Not reported
(38) France	144	25 on ART	15 (10.4%)	Abnormal baseline ALT (p=0.028) and BR levels (p=0.033) Fluconazole use (p=0.008)
(39) Malawi	156	All patients started NVP based ART during TB treatment	3 (2%)	Not reported
(41) Thailand	142	All patients started NVP or EFV based ART	9 (6.3%)	HCV co-infection (aOR 3.03; 95%CI 1.26-7.29)
(42) Ethiopia	353	All patients started ART within 8 weeks of starting TB treatment	106 (30%) Severe DILI: 65 (18.4%)	[3]Female sex (p = 0.001), higher plasma EFV level (p = 0.009), efv/8-hydroxyefavirenz ratio (p = 0.036), raised baseline AST (p = 0.022), and ALT (p = 0.014), lower Hb (p = 0.008), and serum Alb (p = 0.007), NAT2 slow-acetylator genotype (p = 0.039)and ABCB1 3435TT genotype (p = 0.001)

Legend for table 3:
n=number of patients in study
ART: Antiretroviral therapy
DILI: Drug induced liver injury
DILI Total: Drug induced liver injury cases in total
OR: Odds ratio; aOR: Adjusted odds ratio
CI: Confidence interval
ALT: Alanine transaminase; BR: Bilirubin; AST: aspartate aminotransferase;
Alb: Albumin
NVP: Nevirapine; EFV: Efavirenz
HCV: Hepatitis C virus
BMI: Body mass index
Hb: Hemoglogin
[1] Predictors of adverse events reported in this study, not predictors of DILI.
[2]Grade 2 and 3 hepatotoxicity reported here.
[3]Unclear whether this was in univariate or multivariate analysis.

Table 4: Concomitant TB treatment as a risk factor for DILI in patients on ART: Comparing DILI in patients on ART alone vs. patients on ART and TB treatment:

Reference Country	n	DILI among patients on ART only	DILI among patients on concomitant TB treatment and ART	DILI Total	Concomitant TB treatment and ART a significant risk factor for DILI?
(43) South Africa	868	NR	NR	[1]40	Yes
(44) Botswana	310	3%	9%	18	Yes
(45) South Africa	1809	22/?	4/?	26	No
(46) Uganda	240	7/227	3/13	10	Yes
(47) Tanzania	473	15/253 (5.9%)	22/220 (10%)	37	No

Legend for table 4:
n=number of patients in study
ART: Antiretroviral therapy
DILI: Drug induced liver injury
TB: Tuberculosis
DILI Total: Drug induced liver injury cases in total
NR: Not reported
[1]Number of patients with grade 3 or 4 hepatitis reported here.

Burden of antituberculosis and antiretroviral drug-induced liver injury at a secondary hospital in South Africa

Charlotte Schutz, Zahiera Ismail, Charles John Proxenos, Suzaan Marais, Rosie Burton, Chris Kenyon, Gary Maartens, Robert J Wilkinson, Graeme Meintjes

Background. G F Jooste Hospital (GFJH) is a secondary-level referral hospital in a high HIV and tuberculosis (TB) co-infection setting.

Aims. To assess the proportion of significant drug-induced liver injury (DILI) due to tuberculosis treatment (TBT) and/or antiretroviral therapy (ART) among patients presenting with liver dysfunction at GFJH and to describe management and outcomes.

Methods. A retrospective observational study was performed of all cases referred to GFJH with significant liver dysfunction from 1 January to 30 June 2009. Significant liver dysfunction was defined by alanine transaminase (ALT)≥200 U/l or total bilirubin (TBR)≥44 µmol/l. TBT- or ART-associated DILI was defined as significant liver dysfunction attributed to TBT and/or ART and which resulted in the halting of treatment or the adjustment thereof. Outcome measures included case numbers, descriptive data, and in-hospital and 3-month mortality.

Results. A total of 318/354 cases of significant liver dysfunction were reviewed: 71 were classified as TBT- or ART-associated DILI, while liver dysfunction was attributed to other causes in the remainder. In-hospital and 3-month mortality of TBT- or ART-associated DILI patients was 27% (*n*=19) and 35% (*n*=25), respectively. The majority of deaths were related to sepsis or sepsis complicating liver dysfunction. Twenty-three patients (32%) were lost to follow-up; 23 (32%) were alive and in outpatient care 3 months after presentation.

Conclusions. TBT- or ART-associated DILI is a common reason for presentation at a referral hospital in South Africa. In-hospital and 3-month mortality are high. Prospective studies are needed to define optimal management.

S Afr Med J 2012;102(6):506-511.

An estimated 34 million people are HIV-infected globally; South Africa (SA) carries the highest burden with an estimated 5.6 million people infected.[1] A major scale-up of public sector antiretroviral therapy (ART) has seen 1.4 million people start ART,[2] and an increasing proportion of eligible individuals initiating treatment.[3]

Department of Medicine, Faculty of Health Sciences, University of Cape Town, and Infectious Diseases Unit, G F Jooste Hospital, Cape Town
Charlotte Schutz, MB ChB, Dip HIV Man
Suzaan Marais, MB ChB
Rosie Burton, BSc, PhD, MB BS, MRCOG, FCP (SA), Cert ID Phys
Chris Kenyon, MB ChB, MPH, MA, FCP (SA)
Robert J Wilkinson, BM BCh, MA, DTM&H, PhD, FRCP (UK)
Graeme Meintjes, MB ChB, FCP (SA), MRCP, PhD, Dip HIV Man

Infectious Diseases Unit, G F Jooste Hospital, Cape Town
Zahiera Ismail, MB ChB, Dip HIV Man
Charles John Proxenos, MB ChB, Dip HIV Man

Clinical Infectious Diseases Research Initiative, Institute of Infectious Disease and Molecular Medicine, University of Cape Town
Charlotte Schutz, MB ChB, Dip HIV Man
Suzaan Marais, MB ChB
Robert J Wilkinson, BM BCh, MA, DTM&H, PhD, FRCP (UK)
Graeme Meintjes, MB ChB, FCP (SA), MRCP, PhD, Dip HIV Man

Division of Medicine, Imperial College London, UK
Robert J Wilkinson, BM BCh, MA, DTM&H, PhD, FRCP (UK)
Graeme Meintjes, MB ChB, FCP (SA), MRCP, PhD, Dip HIV Man

Division of Clinical Pharmacology, Faculty of Health Sciences, University of Cape Town
Gary Maartens, MB ChB, MMed, FCP (SA), DTM&H

MRC National Institute for Medical Research, London, UK
Robert J Wilkinson, BM BCh, MA, DTM&H, PhD, FRCP (UK)

Corresponding author: *C Schutz (charlottelouw@discoverymail.co.za)*

Tuberculosis (TB) case notifications per annum in SA reached 396 554 in 2010, with 61% of incident TB cases HIV co-infected.[4] TB prevalence is high at initiation of ART: 2 clinics in Cape Town reported concomitant TB treatment (TBT) in 25% and 40% of patients, respectively, at time of ART initiation.[5,6] In SA, 42% of HIV-positive TB cases received both ART and TBT in 2009, compared with 18% in 2008.[3]

Drug-induced liver injury (DILI) is a well-recognised complication of TBT and ART. DILI is frequently encountered at healthcare facilities in SA and is especially challenging to manage in TB/HIV co-infected patients. Hepatotoxicity complicates TBT in 5 - 33% of patients.[7] Studies reporting high rates include patients with subclinical elevations of liver enzymes. Depending on the regimen, hepatotoxicity develops in 9 - 30% of patients receiving ART.[8] HIV infection itself is associated with an increased risk of major TBT side-effects.[9] Liver dysfunction due to TBT or ART carries numerous risks, including: *(i)* direct morbidity and mortality due to liver failure, *(ii)* disease progression due to interruption of optimal therapy, *(iii)* complications of prolonged hospitalisation, and *(iv)* TBT or ART resistance related to interruptions.[10]

G F Jooste Hospital (GFJH), a secondary-level referral hospital in Cape Town, serves communities with a high burden of TB/HIV co-infection. There has been a major scale-up of treatment services for both infections in the hospital's catchment area in recent years. Patients from surrounding primary care HIV and TB clinics with adverse reactions to treatment of either disease, including significant symptoms or signs of liver injury, are referred for management to GFJH.

We aimed to assess the proportion of significant liver dysfunction caused by TBT and/or ART among patients with liver dysfunction presenting to a secondary hospital (GFJH), and to describe management and outcomes.

Methods

A retrospective observational study was conducted and results of all liver function tests (LFTs) performed at the GFJH National Health

Laboratory Service laboratory from 1 January to 30 June 2009 were reviewed. Hepatocellular injury is characterised by a marked rise in serum transaminases, aspartate aminotransferase (AST) and alanine transaminase (ALT). Cholestatic liver injury is characterised by a rise in alkaline phosphatase, gamma-glutamyltransferase and/or raised total bilirubin (TBR).[11] Significant hepatocellular injury and cholestatic injury was defined as resulting in a Grade 3 or 4 elevation of ALT≥200 U/l (>5 times the normal upper limit) and TBR≥44 μmol/l (>2.5 times the normal upper limit), respectively.[12] Patients who fulfilled one or both criteria were included. Sepsis was documented when clinical presentation was compatible and the admitting team managed infection as the primary cause of illness. Hepatic encephalopathy was documented by the admitting team.

Patient records were reviewed and data recorded on a standardised form. DILI was attributed to TBT or ART if either regimen was interrupted or adjusted. Cases not classified as TBT- or ART-associated DILI were classified as 'liver dysfunction due to other causes'. This included: *(i)* patients receiving TBT and ART and diagnosed with hepatic TB-associated immune reconstitution inflammatory syndrome (TB-IRIS), *(ii)* patients presenting with untreated disseminated TB, *(iii)* patients receiving TBT and/or ART and presenting with liver injury with no subsequent change or discontinuation of TBT or ART, and *(iv)* patients diagnosed with alternative causes of liver dysfunction.

The University of Cape Town Human Research Ethics Committee approved the study (HREC ref: 522/2009). Statistical analyses were conducted with STATA 11.1 software (2009).

Management

Patients receiving TBT and ART were managed at primary care clinics according to national treatment guidelines.[13,14] Patients with significant symptoms or signs suggestive of DILI were referred to GFJH. Patients were admitted or managed as outpatients depending on clinical severity and LFT results. GFJH has an infectious diseases referral clinic with capacity to manage stable DILI patients as outpatients.

In patients with TBT-associated DILI, a decision was made to cease treatment temporarily or to switch to alternative and less hepatotoxic treatment. Cessation of TBT was defined as discontinuation of all TBT for longer than a day. In patients whose treatment had been interrupted, a less hepatotoxic regimen, typically consisting of streptomycin, ethambutol and ofloxacin, was usually commenced once LFT results improved. Rifampicin and isoniazid was then 're-challenged' in a stepwise manner after LFT results normalised. Rifampicin or isoniazid was started at a low dose and increased to full dose over a few days with concurrent monitoring of ALT. This was followed by similar introduction of the second drug. Once full-dose rifampicin and isoniazid were re-introduced, certain of the less hepatotoxic drugs were discontinued. Optimal TBT was defined as rifampicin-based therapy.

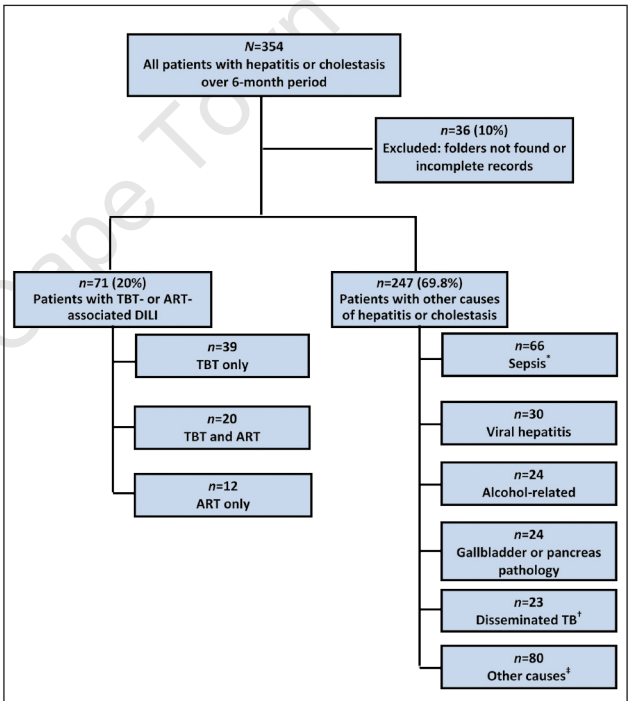
Depending on the suspected cause and severity of ART-associated DILI, generally either: *(i)* ART was ceased, *(ii)* a single drug substitution was made, or *(iii)* more hepatotoxic ART (e.g. nevirapine) was interrupted and replaced within a few days (e.g. by efavirenz 5 - 7 days later), while less hepatotoxic ART (e.g. stavudine and lamivudine) was continued. Optimal ART was defined as triple ART medication from at least 2 classes.

Outcome assessment

Clinical management and outcome data were ascertained by review of patient records. In-hospital and 3-month (within 90 days of presentation) mortality were recorded, including the cause of death where possible. Only in-hospital mortality was recorded for patients with liver injury due to other causes. Three-month retention in care was also recorded. In the case of TBT and/or ART-associated DILI, the Clinicom and eKapa electronic databases were consulted to ascertain follow-up and mortality documented elsewhere in the Western Cape. Loss to follow-up was defined as inability to trace any patient data after discharge, within 3 months of presentation.

Results

A total of 354 patients met the criteria for inclusion; 36 (10.2%) were excluded due to incomplete or missing records. Of 318 cases reviewed, 71 were classified as TBT- and/or ART-associated DILI. In 247 cases, liver injury was attributed to other causes (Fig. 1). Among many other causes of liver injury, the most common was sepsis-induced liver dysfunction, evident from clinical presentation and LFT results; 27 patients receiving TBT or ART were not diagnosed with TBT- or ART-associated DILI because no alteration was made to TBT or ART.



*Twenty-seven (10%) patients in this group were also receiving TBT or ART, but patients presented with a syndrome suggestive of sepsis and were treated for sepsis with no adjustment to TBT or ART.

†Patients presented with jaundice and diagnosis of disseminated TB was made during admission, i.e. patients were not receiving TBT or ART at presentation with liver dysfunction. Cause of jaundice was attributed to TB infiltration of the liver.

‡Including gastro-intestinal tract malignancies, other malignancies with liver metastases, TB-associated immune reconstitution inflammatory syndrome, toxins, cardiac causes with liver congestion, unknown causes (not receiving TBT or ART) and a group of miscellaneous causes (including leptospirosis; echinococcus; amoebiasis; cryptococcosis)

Fig. 1. Hepatitis or cholestasis: description of the cohort. TB = tuberculosis; TBT = TB treatment; ART = antiretroviral therapy; DILI = drug-induced liver injury.

Baseline characteristics

Of the 318 patients, 47% were women and 41% were HIV-infected (Table 1). At presentation, 18% were receiving ART, 26% were receiving TBT and 10% were receiving concomitant TBT and ART. ART regimens included: *(i)* stavudine (or zidovudine), lamivudine and efavirenz (*n*=17; 53%); *(ii)* stavudine (or zidovudine), lamivudine and nevirapine (*n*=9; 28%); and *(iii)* protease inhibitor (PI)-based ART (*n*=4; 13%). Three patients receiving TBT were treated with

Table 1. Baseline characteristics of patients who presented with cholestasis or hepatitis

	Total (*N*=318)	TB or ART* (*n*=71)	Other (*n*=247)
Age (years), median (IQR)	39 (30 - 50)	39 (30 - 43)	39 (29 - 54)
Sex: female, *n* (%)	165 (51.9)	44 (62)	121 (49)
HIV Status			
Tested for HIV, *n* (%)	190 (59.7)	69 (97.2)	121 (49)
HIV-positive, *n* (%)	144 (45.3)	60 (84.5)	84 (34)
HIV-negative, *n* (%)	46 (14.5)	9 (12.7)	37 (15)
CD4 count, median (IQR)	59 (26 - 179)	75 (28 - 189)	57 (26 - 174)
Tested for hepatitis B surface antigen,§ *n* (%)	-	57 (80.3)	-
Positive, *n* (%)	-	8 (11.3)	-
Receiving ART at presentation,¶ *n* (%)	63 (19.8)	32 (45.1)	31 (12.6)
Days of ART, median (IQR)	60 (30 - 251)	41 (29 - 81)	105 (38 - 565)
Receiving TBT at presentation, *n* (%)	92 (28.9)	59 (83.1)	33 (13.4)
Days of TBT, median (IQR)	56 (20 - 129)	40 (15 - 89)‖	99 (32.5 - 158.5)
Regimen I TBT,† *n* (%)	62 (19.5)	44 (62)**	18 (54.6)
Regimen II TBT,‡ *n* (%)	25 (7.8)	12 (17)	13 (39.4)
Concomitant TBT and ART, *n* (%)	36 (11.3)	20 (28.2)	16 (6.5)
Cotrimoxazole prophylaxis documented,†† *n* (%)	127 (39.9)	48 (67.6)	79 (32)
Receiving cotrimoxazole, *n* (%)	59 (18.6)	28 (39.4)	31 (12.6)

*Patients with TBT- and/or ART-associated DILI.

†Regimen I TBT: 2 months of rifampicin, isoniazid, pyrazinamide and ethambutol, followed by 4 months of rifampicin and isoniazid.

‡Regimen II TBT: 2 months of rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin, followed by 1 month of rifampicin, isoniazid, pyrazinamide and ethambutol, followed by 5 months of rifampicin, isoniazid and ethambutol.

§Data were only captured for TBT- or ART-associated DILI.

¶TBT- or ART-associated DILI: 11 known HIV-infected patients with no available information about ART use. Other causes: 1 known HIV-infected patient with no available information about ART use.

‖8 patients with TBT- or ART-associated DILI: unknown duration of TBT.

**11 patients with TBT- or ART-associated DILI: unknown TB regimen.

††Cotrimoxazole prophylaxis documented in known HIV-infected patients.

PI-based ART and thus double-dose lopinavir/ritonavir. In the TBT- or ART-associated DILI category, a history of cotrimoxazole prophylaxis was available in 48/60 (80%) of the HIV-seropositive patients, and of these, 28 (47%) were receiving cotrimoxazole at presentation. Fifty-seven (80%) patients in this category were screened for hepatitis B surface antigen; 8 (14%) were positive.

Clinical presentation and management

Median length of hospital stay was 13 days (interquartile range (IQR) 7 - 20) in the 87% of TBT- or ART-associated DILI patients who were admitted. Patients presented as follows: 56 (79%) with cholestasis (TBR≥44 μmol/l), 31 (44%) with hepatocellular injury (ALT≥200 U/l) and 18 (25%) with both. Fifteen (21%) had hepatic encephalopathy (Table 2). One or more possible alternate causes of liver dysfunction, including sepsis and TB-IRIS, were documented in 53 (75%) of patients.

TBT was ceased in 29 (49%) patients, with a median of 16.5 (IQR 14 - 26) days off optimal treatment. Less hepatotoxic TBT was initiated in 38 (64%) patients prior to re-challenge with rifampicin/isoniazid. Change in ART was individualised and varied widely.

Optimal rifampicin-based TBT was not re-introduced in 27/59 (45.8%) patients who presented while receiving TBT, for the following reasons: *(i)* death (*n*=14), *(ii)* transfer to another facility without particulars of subsequent re-challenge (*n*=5), *(iii)* absence of evidence for initial TB diagnosis (*n*=4), *(iv)* discharge with less hepatotoxic TBT and intention to re-challenge at a later stage (*n*=2), *(v)* presentation of DILI while receiving less hepatotoxic TBT which was continued while ART was adjusted (i.e. managed as ART-associated DILI) (*n*=1), *(vi)* completion of TBT (*n*=1), or *(vii)* patient absconded (*n*=1).

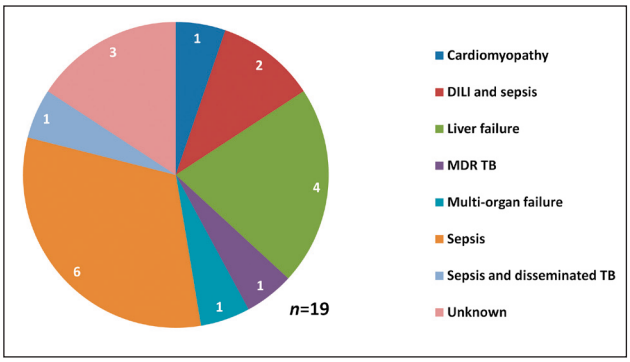


Fig. 2. Cause of in-patient death in TBT- or ART-associated DILI.

ART was interrupted in 11 patients (34%) and altered in 23 (74%). Patients spent a median of 25 (IQR 7 - 40) days off optimal ART (triple therapy). In 27 (38%) TBT- or ART-associated DILI patients, additional investigations were performed, including abdominal ultrasound (*n*=24), computed tomography (CT) of the abdomen (*n*=2), and liver biopsy (*n*=1; performed during DILI relapse).

Patients who were discharged and followed up as outpatients (*n*=21, 29.6%) had a median of 4.5 visits in the 3 months following presentation. Seven (9.9%) patients had subsequent relapse of hepatitis

Table 2. Clinical presentation and management of TBT- or ART-associated DILI patients

	TBT- or ART-associated DILI (*N*=71)
Admitted to hospital, *n* (%)	62 (87.3)
Days in hospital, median (IQR)	13 (7 - 20)
Laboratory results at presentation	
AST (U/l), median (IQR)	245 (117 - 628)
ALT (U/l), median (IQR)	157 (71 - 353)
Patients with ALT≥200 U/l, *n* (%)	31 (43.6)
GGT (U/l), median (IQR)	108 (61 - 292)
ALP (U/l), median (IQR)	110 (80 - 231)
TBR (μmol/l), median (IQR)	88 (50 - 128)
Patients with TBR≥44 μmol/l, *n* (%)	56 (78.9)
Patients with ALT≥200 U/l and TBR≥44 μmol/l, *n* (%)	18 (25.4)
INR performed at presentation, *n* (%)	42 (59.2)
INR, median (IQR)*	1.7 (1.3 - 3)
Clinical features	
Hepatic encephalopathy, *n* (%)	15 (21.1)
Case fatality rate,† *n* (%)	8 (53.3)
Differential diagnosis,‡ *n* (%)	53 (74.7)
Number of differential diagnoses,§ median (range)	2 (1 - 3)
Patients receiving TBT, *n* (%)	59 (83)
Treatment completely interrupted, *n* (%)	29 (49.2)
Less hepatotoxic TBT initiated, *n* (%)	38 (64.4)
TB medication restarted,¶ *n* (%)	32 (54.2)
Days off optimal TBT,‖ median (IQR)	16.5 (14 - 26)
Patients receiving ART, *n* (%)	32 (45)
Treatment completely interrupted, *n* (%)	11 (34.4)
Any change made to ART,** *n* (%)	23 (71.9)
Days off optimal ART,†† median (IQR)	25 (7 - 40)
Additional investigations performed, *n* (%)	27 (38)
USS abdomen	24 (33.8)
CT abdomen	2 (2.8)
Liver biopsy‡‡	1 (1.4)
Outpatient follow-up visits,§§ median (IQR)	4.5 (3 - 7)
Relapse of hepatitis or cholestasis, *n* (%)	7 (9.9)
Admitted to hospital, *n* (%)	5 (7)
Days in hospital, median (IQR)	12 (12 - 21)
Outpatient follow-up visits following relapse,§§ median (IQR)	6 (5 - 8)

AST = aspartate aminotransferase; ALT = alanine transaminase; GGT = gamma-glutamyltransferase; ALP = alkaline phosphatase; TBR = total bilirubin; INR = international normalised ratio.

*Five (7.35%) patients had other reason contributing to high INR: warfarin therapy (*n*=2) and congestive cardiac failure (*n*=3).

†Case fatality rate in patients who presented with hepatic encephalopathy.

‡Patients who had significant differential diagnoses at time of DILI.

§Significant differential diagnoses per patient.

¶Rifampicin and isoniazid restarted.

‖ Rifampicin-based TBT.

**Including ART completely stopped.

††Triple therapy ART.

‡‡One patient had a liver biopsy at subsequent relapse of hepatitis.

§§Outpatient follow-up visits 3 months after presentation.

Table 3. Three-month outcomes of TB- or ART-associated DILI patients* (*N*=71)

	n (%)	Days,† median (IQR)
Died during initial admission§	19 (26.8)	8 (3 - 13)
Discharged; died within 3 months of presentation	6 (8.5)	59.5 (56 - 70)
Lost to follow-up within 3 months of presentation‡	23 (32.4)	42 (18 - 57)
Discharged, alive and in care 3 months after presentation	23 (32.4)	-

*Three months or 90 days from presentation with hepatitis or cholestasis.

†Days from presentation with hepatitis or cholestasis until death or loss to follow up.

‡Lost to follow-up: no patient record available after discharge.

§Three patients who completed TB drug re-challenge died during admission.

or cholestasis; 5 (71.4%) were re-admitted to hospital for a median of 12 days (IQR 12 - 21); 1 died in hospital due to sepsis and 6 were alive and in care 3 months after presentation of relapse.

Patient outcomes

The Kaplan-Meier survival estimate is shown in Fig. 3. In-hospital mortality of the cohort was 27% (*n*=19) and 53% in patients who presented with hepatic encephalopathy. Common causes of death during initial admission included sepsis, a combination of sepsis and active TB or DILI, and liver failure (Fig. 2). Three of 19 in-hospital deaths occurred after completion of TBT re-challenge; causes were sepsis (2) and unknown (1, unexpected death after initial improvement). At 3 months after presentation, 25 (35%) patients had died, 23 (32%) were alive and in care, and 23 (32%) were lost to follow-up (Table 3).

In cases of 'liver dysfunction due to other causes', 71 (28.7%) patients died during admission. This included 34 patients admitted with sepsis, of whom 14 were receiving TBT or ART.

Discussion

To our knowledge, this is the first study describing the management, outcome and high burden of TBT- or ART-associated DILI at a referral hospital in a high TB/HIV prevalence community. Over 6 months there were 71 cases. This may reflect under-ascertainment, accepting that – in the absence of a confirmatory test for DILI – some patients admitted with TBT- or ART-associated DILI would have been misclassified as having other causes of liver dysfunction such as TB-IRIS or sepsis.

TBT was a frequent cause of DILI in our study. TBT-attributed DILI may reduce TBT effectiveness due to a negative effect on adherence, treatment interruption and substitution with less effective TB medication. TBT-associated DILI may be fatal if not recognised and managed early.[10]

We attributed DILI to ART in 23/32 patients receiving such therapy. Medication of both first- and second-line ART regimens

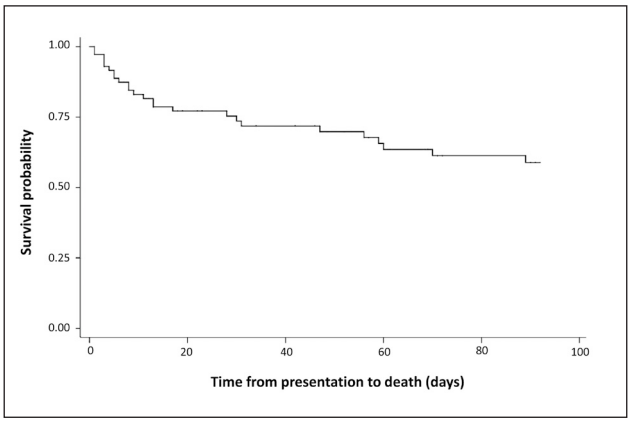


Fig. 3. Kaplan-Meier survival estimate in TBT- or ART-associated DILI.

may cause DILI. Nucleoside reverse transcriptase inhibitors (NRTIs) may cause fatty liver related to mitochondrial toxicity. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) cause liver injury related to immune-mediated hypersensitivity. The mechanism of PI-induced DILI is not entirely understood.[8] In patients receiving lopinavir/ritonavir, additional ritonavir or double-dose lopinavir/ritonavir is required to counteract rifampicin induction, and high incidence of hepatotoxicity has been reported in such patients.[15,16] Three patients were receiving lopinavir/ritonavir-based ART and TBT; 2 were alive and in care 3 months after presentation and 1 was lost to follow-up.

Twenty patients were on concomitant rifampicin-based TBT and ART, which have overlapping toxicities. The cause of liver dysfunction in these patients is likely multi-factorial. The pathogenic mechanisms of DILI are complex, unpredictable and related to medication and genetic factors.[11,17] Management is complex and needs to be individualised. TBT or ART was ceased or altered in all 20 cases, leading to prolonged hospital admission for drug re-challenge and increased vulnerability to disease progression and other infections. There are considerable risks associated with prolonged hospital stay in the context of advanced HIV infection, particularly nosocomial sepsis.[18] We observed more cases of DILI related to TBT alone (*n*=39) than with ART alone (*n*=12) or concomitant ART and TBT (*n*=20), possibly reflecting that more patients were initiated on TBT than on ART in the hospital catchment area during the study period. Alternatively, TBT may be a more common cause of DILI.

Adding to the complexity, cotrimoxazole may also cause DILI; prophylactic treatment is often stopped during management of DILI, rendering patients vulnerable to opportunistic infections. Chronic hepatitis B is also an important co-factor in DILI; concomitant TBT significantly increases the risk of hepatotoxicity.[19] Hepatitis B surface antigen was positive in a minority of cases in our study; 8/57 patients with TBT- or ART-associated DILI.

A striking finding was the high mortality associated with TBT- or ART-associated DILI (35% at 3 months after presentation) with a median time to death of 11 days (IQR 5 - 31). Mortality was likely under ascertained, as it is possible that some patients recorded as lost to follow-up really died. In comparison, mortality in a general cohort of patients with HIV-associated TB in our setting was only 8% during 6 months of TBT.[20]

In our study, the most common cause of death ascertained was sepsis, highlighting the vulnerability of patients with liver injury to bacterial and other infections. Close monitoring for community- and hospital-acquired bacterial infections and early diagnosis with appropriate antimicrobial treatment may improve outcome. Liver failure was the cause of death in only a minority of cases. Further studies are required to define reasons for the high mortality among DILI patients; this rate may reflect direct and indirect consequences

of DILI, or that DILI complicates poor prognoses owing to other disease-related factors.

We acknowledge several limitations of our study. The use of herbal, traditional or over-the-counter medication, all of which may cause liver injury, was poorly documented. A retrospective review has many limitations: data capture was limited to documentation by attending clinicians and 10% of records were not found for review.

Conclusions

Liver injury due to TBT- or ART-associated DILI necessitating referral to hospital was common and associated with high mortality in our study. The cause of liver injury in HIV-TB co-infected patients is likely multi-factorial and is complex to manage. Prospective studies are urgently needed to investigate optimal management strategies and improve outcomes of such patients. The use of early invasive investigations (e.g. liver biopsy) in the diagnosis and management of liver injury requires investigation.

Acknowledgements. Sources of support: Perinatal HIV Research Unit, the US Agency for International Development, and the President's Emergency Plan for AIDS Relief (SM and CS), Wellcome Trust (RJW and GM, WT 081667, 084323 and 088316); a Fogarty International Center South Africa TB/AIDS Training Award (GM and CS, NIH/FIC 1U2RTW007373-01A1, U2RTW007373 ICORTA); a European Union Grant (RJW, SANTE/2005/105-061-102); and MRC (RJW, U1175.02.002.00014.01). The funders had no role in study design, data collection and analysis, decision to publish, or manuscript preparation.

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Accepted 27 January 2012.

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Journal references:
Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289:350-355. [http://dx.doi.org/10.1000/hgjr.182] [PMID: 2764753]

Book references:
Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.

Chapter/section in a book:
Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

Internet references:
World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

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PART D: Appendices:

a. Acknowledgements:

Co-authors:

Graeme Meintjes, Robert J Wilkinson, Gary Maartens, Suzaan Marais, Rosie Burton and Chris Kenyon were all involved with study conception and planning of the study. Zahiera Ismail and Charles John Proxenos assisted with design and piloting of the data capture sheets. They also helped to capture data and with data entry. Graeme Meintjes and Suzaan Marais helped with reviews of the first rough drafts of the paper and Suzaan Marais helped with extensive reviewing of the second last draft of the paper. Graeme Meintjes reviewed the final draft extensively. This final draft was then reviewed by all co-authors and extensive input was given to finalize the paper for submission. All co-authors' comments were incorporated into the paper prior to submission.

Sources of financial support (no support was specifically for this study):

Perinatal HIV Research Unit, the US Agency for International Development, and the President's Emergency Plan for AIDS Relief (Suzaan Marais and Charlotte Schutz). Wellcome Trust (Robert J Wilkinson and Graeme Meintjes, WT 081667, 084323 and 088316). Fogarty International Center South Africa TB/AIDS Training Award (Graeme Meintjes and Charlotte Schutz, NIH/FIC 1U2RTW007373- 01A1, U2RTW007373 ICORTA). A European Union Grant (Robert J Wilkinson, SANTE/2005/105-061-102). MRC (Robert J Wilkinson, U1175.02.002.00014.01). The funders had no role in study design, data collection and analysis, decision to publish, or manuscript preparation.

Thank you:

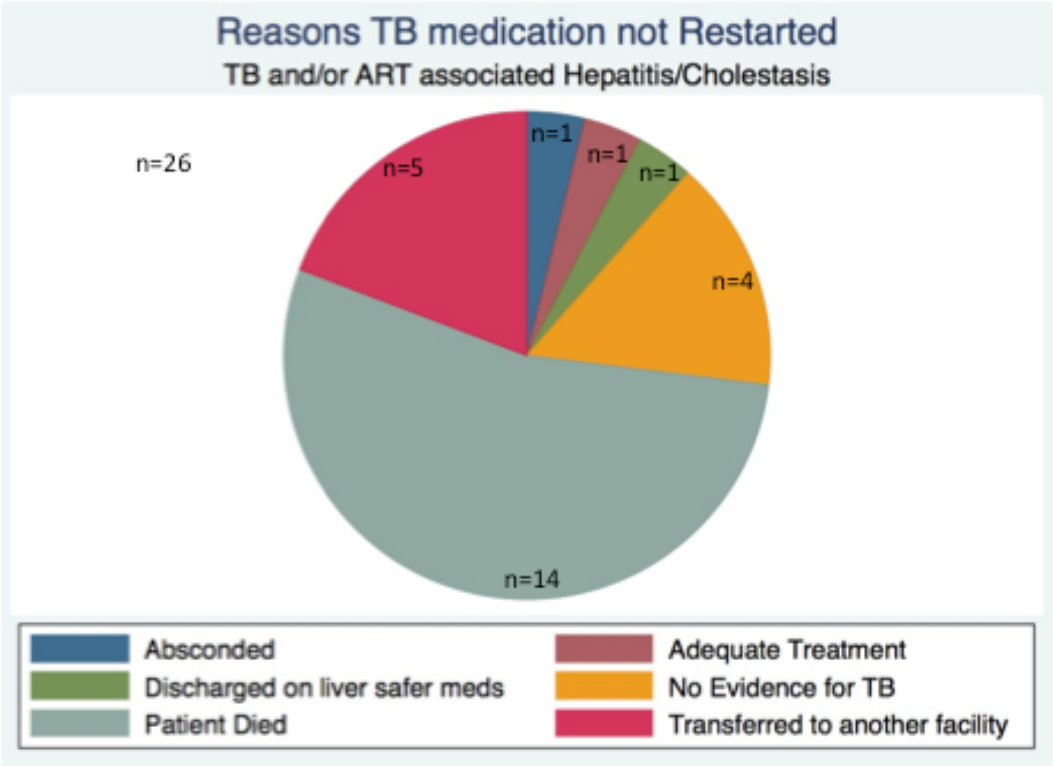
I would like to extend a special thank you to my supervisor Graeme Meintjes for all his patient support, advice and review of material throughout this project.

Also to all my lecturers throughout the MPH (Clinical Research) course who have taken the time to teach me the basic concepts of sound clinical research methods.

b. Selected tables or figures:

The following figure and table were prepared for the manuscript but was not submitted due to space constraints. Some of the information was included in the flow chart and the text in the manuscript.

Figure: Reasons treatment for tuberculosis was not restarted in patients who had treatment interruption for tuberculosis and or antiretroviral treatment associated liver dysfunction.



Legend:
n: Number of patients in this category.
TB: Tuberculosis treatment
ART: Antiretroviral treatment

Table: Other Causes of Liver Dysfunction:

Cause n=249	**Frequency**	**Percentage (%)**
⁎Sepsis	66	26.5
⁎⁎Viral Hepatitis	31	12.5
Alcohol	24	9.6
Gallbladder/Pancreas pathology	24	9.6
Disseminated TB	23	9.2
Other	23	9.2
Malignancy	22	8.8
Unknown	12	4.8
⁎⁎⁎Cardiac	11	4.4
Cotrimoxazole	5	2
TB IRIS	4	1.6
Paracetomol	3	1.2
Toxins	1	0.4

TB: Tuberculosis
TB IRIS: TB Immune Reconstitution Inflammatory Syndrome.
⁎ This includes patients who had bacteriologically proven sepsis and also patients with a clinical picture of sepsis who were managed as sepsis by the admitting team.
⁎⁎ This includes acute hepatitis A and acute and chronic cases of hepatitis B.
⁎⁎⁎ Cardiomyopathy or congestive cardiac failure causing liver congestion and abnormal liver function tests.